A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy

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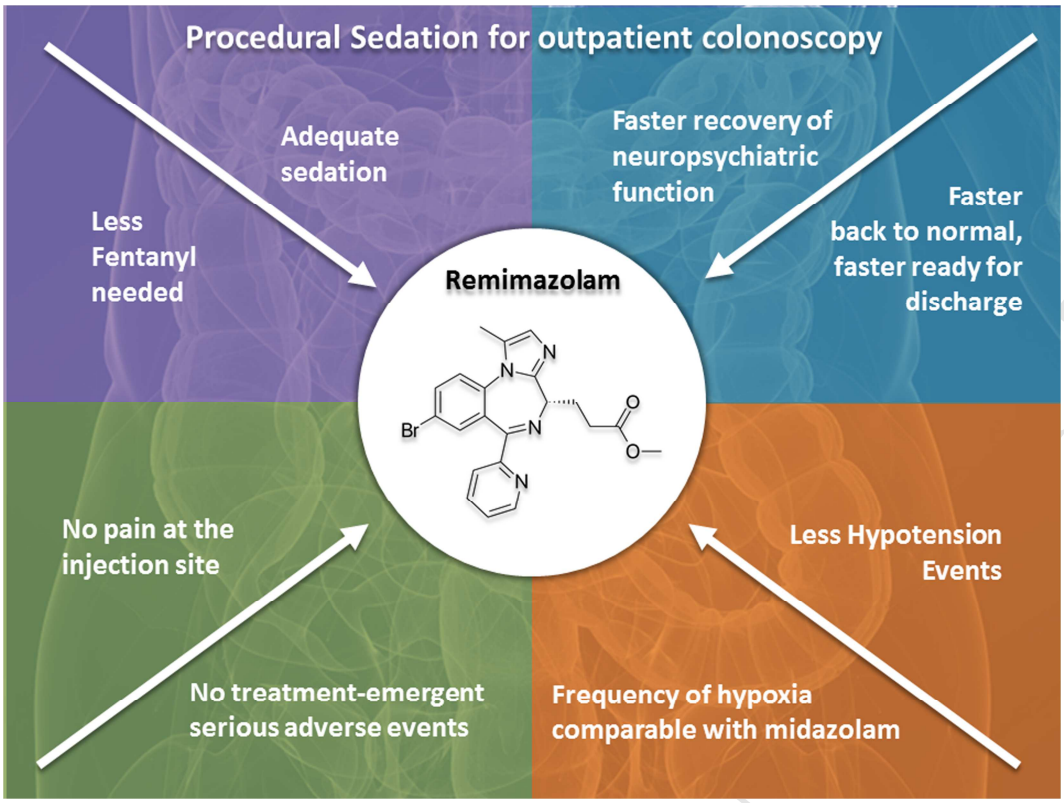

Abbreviations

- AEs (adverse events)
- BMI (body mass index)
- BP (blood pressure)
- FDA (Food and Drug Administration)
- HVLT-R (Hopkin's Verbal Learning Test)
- ITT (Intention to Treat population)
- mITT (modified Intention to Treat population)
- MOAA/S (Modified Observer's Assessment of Alertness/Sedation),
- SpO_2 (mean oxygen saturation level)
- PP (Per Protocol population)

Abstract

Background: Remimazolam is an ultrashort-acting benzodiazepine.

Methods: We performed a randomized double-blind comparison of remimazolam to placebo for outpatient colonoscopy. This study design was a requirement of the U.S. Food and Drug Administration. An additional group was randomized to open-label midazolam administered according to its package insert instructions (randomization ratio for remimazolam:placebo:midazolam was 30:6:10). Study medications were administered under the supervision of the endoscopist, without any involvement of an anesthesia specialist. Patients were given 50 to 75 μg of fentanyl before receiving study medications. Patients who failed to achieve adequate sedation in any arm were rescued with midazolam dosed at the investigator's discretion. The primary endpoint was a composite that required 3 criteria be met: completion of the colonoscopy, no need for rescue medication, and ≤5 doses of remimazolam or placebo in any 15-minute interval (≤3 doses of midazolam in any 12-minute interval in the open-label midazolam arm).

Results: There were 461 randomized patients in 12 U.S. sites. The primary endpoint was met for remimazolam, placebo, and midazolam in 91.3%, 1.7%, and 25.2% of patients, respectively ($P < 0.0001$ for remimazolam vs placebo). Patients administered remimazolam received less fentanyl, had faster recovery of neuropsychiatric function, were ready for discharge faster, and felt back to normal faster than patients with both placebo and midazolam. Hypotension was less frequent with remimazolam and hypoxia occurred in 1% of subjects with remimazolam or midazolam. There were no treatment-emergent serious adverse events.

Conclusion: Remimazolam can be safely administered under the supervision of endoscopists for outpatient colonoscopy and allows faster recovery of neuropsychiatric function compared with placebo (midazolam rescue) and midazolam.

Introduction

Endoscopic sedation is generally based on either midazolam or propofol, with the percentage of cases in the United States using propofol significantly increasing over the past two decades [1,2].

Midazolam is usually given with an opioid [1]. Advantages of midazolam include excellent amnesia, easy titration, and widespread acceptance of administration by endoscopists. Disadvantages of midazolam include greater cumulative effects due to a long-acting metabolite that causes slow recovery of neuropsychiatric function relative to propofol [3,4].

Propofol can be administered in combination with an opioid and/or benzodiazepine, and titrated to moderate sedation [5]. Propofol has a rapid onset and offset of action and there is a widespread perception that its advantages are maximized when administered as a single

agent, which usually results in deep sedation and has led to restrictions that frequently confine its administration to anesthesia specialists. The increasing use of propofol for endoscopic sedation is associated with improved patient satisfaction [6], but is not cost-effective with regard to safety endpoints [7], and has been associated with high rates of aspiration pneumonia [8,9].

Remimazolam is an ultrashort-acting benzodiazepine in development for procedural sedation [10]. Like midazolam, remimazolam acts on GABA receptors to induce sedation. Unlike midazolam, remimazolam is metabolized by tissue esterases. Remimazolam differs from all other benzodiazepines by its carboxylic ester linkage, enabling its rapid breakdown to inactive metabolites only. The mean terminal elimination half-life of remimazolam is 0.75 hours, and that of midazolam is 4.3 hours [11,12]. In phase II trials, remimazolam provided adequate procedural sedation for endoscopy, and faster recovery, than midazolam [13,14].

We describe a prospective, randomized, parallel group study comparing remimazolam to placebo (blindly). The comparison to placebo was required by the U.S. Food and Drug Administration (FDA), which sought data on the performance of fentanyl plus remimazolam compared with fentanyl alone. To provide information on the relative performance of remimazolam and midazolam, we included an open-label arm of midazolam. However, the FDA required that midazolam be administered according to its package insert. Thus, neither the placebo arm nor the midazolam arm reflect usual clinical practice. The study was initiated at 13 sites in the United States (with 12 contributing patients), in patients with American Society of Anesthesiology risk class I to III. All patients received an initial dose of 75 μg of fentanyl (plus repeated 25 μg

top-up doses to a total of up to 200 μg) during the first 80% of the study, which we lowered to 50 μg for the last 20% of the study. All sedation was given under the supervision of the endoscopist.

Methods

Overall design

This study was a prospective, randomized, placebo and active controlled, multicenter, parallel group study comparing remimazolam to placebo in a double-blind manner, with an open-label midazolam arm. The composite primary endpoint and secondary endpoints for the sedation level are summarized in Table 1. The blinded comparison of remimazolam to placebo was requested by the US FDA. Patients were undergoing diagnostic or therapeutic colonoscopy. Four hundred and sixty-one patients were randomized into one of three groups: remimazolam, placebo, or open label midazolam in a ratio of 30:6:10.

Figure 1 shows the flow of the study design. Supplementary Table 1 shows the procedures performed at each visit. All participating sites obtained Institutional Review Board approval for participation. Patients were recruited between April 2015 and April 2016. The trial was registered at ClinicalTrials.gov with registration number NCT02290873.

On the day of colonoscopy, all patients received up to 1,000 mL of 0.9% NaCl solution as an intravenous (IV) drip starting before the procedure. All patients received fentanyl before the assigned study sedative medication. For the first 80% of the study, patients received an initial dose of 75 μg of fentanyl (or a suitably reduced dose for elderly and debilitated patients). For the last 20% of the study, the initial fentanyl dose was reduced

to a maximum of 50 μg. This change was made at the request of the Data Safety Monitoring Board because the number of patients in the placebo/remimazolam group in the pre-amended portion of the study had transiently reached Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S: see Table 2) scores of 0 could be regarded a safety issue, although no safety signal was associated with low MOAA/S scores.

Supplemental oxygen at a rate of 4 L/min was administered to all patients before any medication and until the patient was fully alert (defined as 3 consecutive MOAA/S scores of 5). Patients were randomized to receive an initial single intravenous dose of remimazolam 5.0 mg or an equal volume of placebo over one minute in a blinded manner and colonoscopy was initiated when adequate sedation (MOAA/S ≤3) was achieved. Sedation was maintained by injection of further top-up doses of remimazolam 2.5 mg (1 mL) or an equal volume of placebo not earlier than two minutes apart after assessment of the sedative effect. For the maintenance phase of sedation, adequate sedation was pre-defined as a MOAA/S of ≤4 in all study arms. The overall number of remimazolam/placebo doses was limited to 5 doses in any 15 minute window. If 5 doses (including the initial bolus) within any 15-minute window were not sufficient to obtain or maintain adequate sedation, the patient was designated a treatment failure.

The overall number of midazolam doses was limited to three doses in any 12-minute window (as per the midazolam package insert: 1 dose equals 1 mg for a subject <60 years and 0.5 mg for those ≥60 years, debilitated or chronically ill). More than 3 doses required to obtain or maintain adequate sedation for colonoscopy within any 12-minute window was designated a treatment failure.

After determination of treatment failure in any study group, midazolam was the only sedative medication (rescue medication) permitted to complete the colonoscopy. Once a patient was designated a treatment failure, the dosing of rescue midazolam was at the endoscopist's discretion. After the initial dose of fentanyl, pain alone during colonoscopy could be treated by top-up doses of fentanyl 25 μg every 5 to 10 minutes with a maximum dose of 200 μg. Fentanyl could not be administered if the respiratory rate was < 8 breaths/minute or the oxygen saturation level S_pO_2 was < 90%.

Eligibility of study subjects

The inclusion and exclusion criteria are listed in Table 3.

Pre-procedure assessments

Before initial administration of trial medication, patients underwent bowel preparation for colonoscopy, in accordance with the local standard bowel preparation protocol, baseline physical examinations were performed, hemodynamics and respiratory parameters, baseline MOAA/S score and HVLT-R were assessed, and baseline drowsiness was recorded. Preprocedure assessments are detailed in SupplementaryTable 1.

Randomization and unblinding

The randomization schedule was computer-generated using a permuted block algorithm. Randomization was assigned sequentially as patients entered the study without site stratification. Treatment unblinding was permitted only in a medical emergency. For patients assigned to remimazolam and placebo, all study personnel other than the pharmacist were blinded to the study agent throughout. Only the midazolam arm was open label.

Intraprocedure assessments

After start of study drug administration, MOAA/S scores were recorded at 1, 1.5, 2, 2.5, and 3 minutes and further in 1-minute intervals until fully alert. After fully alert, MOAA/S scores were recorded every 5 minutes until Ready for Discharge, then every 10 minutes (up to 90 minutes) until actual discharge (Supplementary Table 1).. Nadirs of heart rate, respiratory rate, and SpO_2 were determined by continuous recording using Nellcor (Medtronic, Minneapolis, Minn) monitors. Implausible values were excluded from the analysis, based on the measurement range of the Nellcor machine (ranges were defined as follows: SpO_2: 60% - 100%; pulse: 20 - 200 beats/minute; respiratory rate: 4-40 breaths/min), as well as based on pre-defined "usable Nellcor data." A Nellcor vital sign measurement was considered "usable" if measurements were within the defined ranges, there was no delay >2 minutes between start of study medication and start of Nellcor assessment, and at least 90% of readable Nellcor data (per parameter) within the observation time were available. Capnography was not used.

Post-procedure assessments

"Fully alert" was defined as the first of 3 consecutive MOAA/S measurements of 5 after the completion of the procedure. No attempt was made to wake the patient prematurely upon completion of the procedure. Blood was drawn for hematological and chemistry tests immediately before discharge and at follow-up.

Safety assessments

Safety was assessed by physical examination, vital signs (supine heart rate, systolic, diastolic, and mean BP, respiration rate and temperature), ECG, full blood count, standard chemistry panel, assessment of pulse oximetry measurements, pain on injection intensity rating, airway interventions (chin lift, jaw thrust, requirement of repositioning,

and/or manual or mechanical ventilation), and administration of additional fluids or medication or any interventions necessary due to a clinically relevant change in ECG.

The following were considered adverse events (AEs).

- Bradycardia: <40 beats/minute or a drop in heart rate of 20% or more from baseline that lasted continuously for ≥30 seconds.
- Hypertension: systolic BP ≥180 mm Hg or diastolic BP to ≥100 mm Hg, or an increase of systolic or diastolic BP of 20% or more over baseline or necessitating medical intervention.
- Hypotension: systolic BP ≤80 mm Hg or diastolic BP ≤40 mm Hg, or a fall in systolic or diastolic BP of 20% or more below baseline or necessitating medical intervention.
- Respiratory rate decrease: < 8 breaths/minute.
- Hypoxia: Oxygen saturation <90% for ≥1 minute, or any drop necessitating medical intervention.
- Prolonged sedation: MOAA/S ≤4 for longer than 60 minutes after the last dose of study drug, including the need to administer flumazenil (at the investigator's discretion).

The following ECG parameters were collected: PR interval, RR interval, QRS interval, QT interval, and QTc interval (QT corrected, using Bazett and Fridericia formulae).

All available study data were reviewed by a Data Monitoring Committee at 2, 4, 6, and then every 3 months after initiation of recruitment.

The planned summary analysis of the incidence of MOAA/S scores (0-5) at select timepoints and an exploratory post-hoc analysis were performed. The aim of the

exploratory analysis was to assess the co-variance of MOAA/S scores with vital signs such as respiratory rate, heart rate, or SpO_2. Every MOAA/S score reported was matched either with a corresponding vital sign value documented by the endoscopist or the nadir value of the Nellcor reported vitals (see Supplementary Table 2 for defined study populations).

Sample size and power

Sample size calculations for this superiority trial were based on the following assumptions: For a one-sided type I error rate of 0.025 and a target power of 90%, the assumption of a success rate of 30% for the placebo group and 90% for the remimazolam group led to sample sizes of 15 patients per treatment group. However, in order to reach an appropriate size for the safety database, 300 patients were required for the remimazolam group. The placebo group was set at 60 patients in order to avoid overly unequal group sizes. The power attained at different success rates for the placebo and remimazolam groups (type I error rate fixed as 0.025) is shown in Supplementary Table 3. The midazolam group, which was not part of the primary confirmatory analysis, but is included for assay sensitivity, was set at 100 patients.

Statistical methods

All safety analyses presented in our current article were conducted on patients in the safety population whereas all efficacy analyses were performed on patients in the ITT population (Supplementary Table 2). The primary efficacy analysis was summarized descriptively for overall success and within each category for treatment group. Efficacy significance testing of time to event analyses were performed in a descriptive manner using the log rank test. For secondary efficacy variables descriptive summaries (n, mean,

SD, median, minimum, and maximum) were provided. Overall and pairwise comparisons at each time point were made using ANOVA models with treatment as the main effect.

Results

Randomization

A total of 461 patients were randomized at 12 sites, including 298 to remimazolam, 60 to placebo, and 103 to open label midazolam. The mean age for the entire population was 54.4 (+/- 10.12) years and 50.3% were female. Table 4 shows the mean age, sex, ethnicity, race, and body mass index (BMI) for patients (safety set) in the 3 study groups. There were no significant differences between the study groups for any demographic factor. No unblinding occurred.

Primary efficacy variable

Procedure success rates for the study groups and the rates at which each of the three components of procedure success (Table 1) were satisfied are shown in Table 5. Remimazolam was superior to placebo for overall procedural success, for lower or no need for a rescue medication, and for lower number of top-up doses required. The difference in success rates was 0.896 (95% CI, 0.851 - 0.942), with a significant difference between the two treatment groups (P<0.0001; Table 5).

Fentanyl dosing

The percentage of patients in each study group who received a 75 µg dose was similar between the study arms (Table 6). The total mean dose of fentanyl and the mean number of fentanyl top-ups were each lower with remimazolam (88.6 µg, 0.76) compared with placebo (121.3 µg, 1.93) and midazolam (106.9 µg, 1.34). The change in the mean

number of top-up doses of fentanyl administered after the initial dose of fentanyl was reduced from 75 μg to 50 μg was not remarkable.

Pain at injection site

When a VAS was used, the mean pain score for remimazolam for pain at the injection site (4.9) was not significantly different from placebo (5.7; p=0.5902). The midazolam VAS pain score was 5.8.

Sedative dosing

The mean dose of remimazolam administered was 10.53 (± 3.98) mg, median 10.0 mg. Patients in the remimazolam arm received a mean of 2.22 (± 1.59) top-up doses of sedative, with a mean of 5.07 (± 0.55) for patients in the placebo arm and 2.97 (± 1.08) in the midazolam arm. Patients who did not require rescue sedative medication in the open-label midazolam received a mean of 4.30 (± 1.62) mg of midazolam.

Procedure times

The time from the start of medication administration to reaching a MOAA/S of 3 largely reflects the study protocol, and was shorter for remimazolam at 5.1 (± 3.82) minutes compared with placebo 20.3 (± 4.34) minutes and less than midazolam 16.9 (± 6.31) minutes.

Time to peak sedation, defined as time to the lowest MOAA/S score for the patient before the first top-up dose, was median 3.0 minutes (95% CI: 2.0, 3.0) in the remimazolam group. In the placebo group and the midazolam group, the median time to peak sedation could not be estimated as the majority of patients needed rescue sedative medication. The median time to start of procedure was shorter at 4.0 minutes in the remimazolam group

compared with placebo (19.5 minutes; 95% CI, 18.0; 21.0; $p < 0.0001$) and the midazolam group (19.0 minutes; 95% CI, 17.0; 20.0).

Sedation level

The MOAA/S scores according to procedure time are shown in Supplementary Figure 1. The mean deepest MOAA/S score for the entire 461 patients was 2.12 (± 1.14). The mean deepest MOAA/S score by treatment group was 1.95 (± 1.18) for remimazolam, which was lower than placebo 2.25 (± 0.97) and midazolam 2.54 (± 0.93). During the first 80% of the study, more patients in remimazolam group, as compared with those in the placebo and midazolam groups, reached MOAA/S scores of 0. Although these MOAS/S scores were not associated with any serious AEs, the Data Safety Monitoring Board recommended that the starting fentanyl dose be reduced to 50 μg for the remaining 20% of the study. After this dose reduction, the mean deepest MOAA/S score was not different from the mean deepest MOAA/S with remimazolam before the change. However, (1) the number of patients who reached MOAA/S scores of 0 was reduced to a level comparable with midazolam at the labeled dose and (2) the standard deviation was significantly smaller after fentanyl dose reduction (Supplementary Figure 1).

The exploratory post-hoc analysis focused on co-variance of vital signs and the depth of sedation (MOAA/S score) (Supplementary Figure 2). Overall no positive correlation was found between the depth of sedation and the reported vital signs (respiratory rate, heart rate, and SpO_2). The Nellcor reported vital signs were analyzed separately by pooling them into groups based on the sedation level of the subject at the specific time-point of vital sign assessment. This resulted in 3 comparable vital sign datasets: vitals assessed

during the time interval when subject experienced MOAA/S 0-1, MOAA/S 2-4, and MOAA/S 5, respectively.

Recovery times

Table 7shows recovery times for the 3 study groups. Recovery times were consistently shorter for remimazolam compared with placebo (P<0.001). The reported mean time from the end of the procedure to patients feeling completely "back to normal" was 3.2 hours in the remimazolam group, compared with 5.8 hours with placebo (hazard ratio of 1.750; 95% CI, 1.311 - 2.336; P=0.0001). Mean recovery time was 6.1 hours in the midazolam group.

Recovery of neuropsychiatric function

There were no differences between study groups in the HLVT-R total raw scores, delayed recall, retention raw scores, or recognition discrimination at baseline. Table 8 shows the comparison of Hopkins scores between the different treatment arms at 5 minutes after the patient was judged fully alert. All the scores demonstrated better restoration of neuropsychiatric function after remimazolam compared with placebo and midazolam.

Recall

When the Brice questionnaire was used within 10 minutes of the patient reaching fully alert status, the percent of patients who said yes to the question "Can you remember anything?" was 29.2% for remimazolam, 28.3% for placebo, and 31.1% for midazolam. On the fourth visit, the scores for recall of the procedure (0=none of the procedure remembered and 10=all of it), showed a mean remimazolam score of 1.9, placebo 1.7, and midazolam 1.6. For the fourth visit follow-up Brice questionnaire VAS for satisfaction (0=completely dissatisfied; 10=completely satisfied), the mean remimazolam

score was 9.6, placebo 9.4, and midazolam 9.5. For the question, “Did you experience any untoward effects the day after the procedure,” the percent of patients who answered “yes” was 6.0% for remimazolam, 11.7% for placebo, and 7.8% for midazolam.

Safety

Table 9 lists the incidence of AEs and treatment emergent AEs for the 3 study groups. The incidence of hypotension was 61.8% with midazolam, 41.7% for placebo and 38.9% for remimazolam. The incidence of hypotension was the principal contributor to the main differences observed in treatment emergent AEs between remimazolam and midazolam.

At the screening examination and the baseline examination, there were no differences among groups in body temperature, heart rate, systolic or diastolic BP, or oxygen saturation. The rates of treatment emergent AEs with remimazolam, placebo, and midazolam were 73.6%, 78.3%, and 91.2%, respectively ($P<0.0001$ remimazolam vs midazolam). Table 10 shows the nadirs for heart rate, respiratory rate, and oxygen saturation for the three groups. All of the mean nadirs were numerically lower with placebo and midazolam compared with remimazolam, except for oxygen saturation, which was not different between the arms.

Laboratory safety parameters showed no clinically meaningful differences between treatment groups in the incidence of out-of-range values, all of which appeared related to bowel preparation.

Discussion

We report the results of a randomized, placebo-controlled, multicenter study comparing remimazolam to placebo in a blinded fashion and to an open label arm of midazolam, in outpatients undergoing colonoscopy. The study design was driven by consultation with

the FDA, and evaluated the sedative effect of remimazolam plus fentanyl to fentanyl alone. Because fentanyl is seldom administered in clinical practice as a single agent for colonoscopy, we elected to add a randomized, but open label, arm of midazolam in order to have an assessment of how remimazolam plus fentanyl compared with midazolam plus fentanyl, as the latter is a very commonly used sedative/analgesic combination in current colonoscopic practice. After consultation with FDA, we administered midazolam in the midazolam open label arm according to the instructions in the United States midazolam package insert, which is understood to be a slower and more cautious administration regimen for midazolam than is commonly used in clinical practice. Thus, the times to achieve various sedation endpoints in this study are likely prolonged in the placebo and midazolam arms because of the study protocol and may overstate the advantages of remimazolam with regard to the onset of the sedation. Conversely, the results likely understate the advantages of remimazolam for recovery because midazolam is generally administered more rapidly and in higher doses in clinical practice. Despite these limitations in study design, the study provides useful information about remimazolam as a sedative for colonoscopy. The key finding is that fentanyl 50 to 75 μg, followed by remimazolam at an initial dose of 5 mg and subsequent doses of 2.5 mg as needed, resulted in adequate sedation for outpatient colonoscopy. The mean total dose of remimazolam used was 10.5 mg, indicating that the initial dose and 2 top-ups of remimazolam are sufficient for sedation in average patients. Importantly, remimazolam showed the most rapid values for recovery of neuropsychiatric function, readiness for discharge, and return to a feeling of complete normality consistent with previous data [14]. Remimazolam did not produce pain at the injection site but produced amnesia for the

procedure comparable to midazolam. Finally, remimazolam resulted in no serious AEs. The absolute rates of AEs were higher in all arms of the study compared with previous trials [14], but this likely reflects differences in definitions of AEs between studies. In the absence of serious AEs, the most important observation regarding AEs are the comparison of AE rates between study arms. The rate of hypotension was lowest with remimazolam and the rate of hypoxia with remimazolam was comparable to the rate of hypoxia with midazolam.

During the study, we lowered the usual dose of fentanyl given before any sedative from 75 μg to 50 μg (at the recommendation of the Data Safety Monitoring Board). This was done because the number of patients that reached MOAA/S of 0 was considered a potential concern, although neither serious AEs were nor relevant changes in cardio-respiratory parameters had been observed. This is consistent with the findings of Kim et al [15], which indicate that no response to a trapezius squeeze indicates the transition to anesthesia rather than representing surgical anesthesia. Reducing the dose of fentanyl reduced the occurrence of MOAA/S of 0 in this study to that of the low dose of midazolam recommended in its package insert.

Reducing the dose of fentanyl from 75 μg to 50 μg did not adversely affect the advantageous features of remimazolam. This reduced dose of fentanyl and reduction of MOAA/S scores of 0 should improve the acceptability of remimazolam administration by non-anesthesia specialists. With regard to sedation by remimazolam, we note that like other benzodiazepines, the sedative effects are reversible with flumazenil.

During an exploratory analysis it was also demonstrated that vital signs do not correlate with MOAA/S scores, which is in agreement with the assessment of all Phase III studies

at the time of the decision to reduce the fentanyl dose. The same analysis stratified by treatment arms showed low variance of vital sign values in the remimazolam group, ranging between those reported for the midazolam and placebo group.

In summary, remimazolam is a safe and effective sedative for outpatient colonoscopy when administration is supervised by endoscopists and allows more rapid recovery compared with placebo and midazolam. Remimazolam offers benefits to patients and endoscopists compared with midazolam, and the potential for lower costs to patients and insurers compared with propofol administered by healthcare providers trained in providing general anesthesia.

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Tables

Table 1: Primary and Secondary Outcome Variables

Primary outcome measure

- Success of procedure as measured by
- Completion of colonoscopy and
- No requirement for an alternative sedative and
- In the case of remimazolam and placebo, no requirement for more than 5 top-ups of study medication within any 15-minute period. In the case of midazolam, no requirement for more than 3 doses in any 12-minute window.

Secondary objectives

- Time to start of procedure after administration of the first dose of medication
- Time to peak sedation after administration of the first dose of medication
- Times to readiness for discharge after the end of procedure
- Times to fully alert (first of 3 MOAA/S scores of 5 after end of procedure)
- Recall of the procedure by the Brice questionnaire when fully alert and on Day 4
- Changes to the patient's cognitive function by the HVLT-R administered before study medication and after fully alert
- Safety of multiple doses of remimazolam after a standard dose of fentanyl
- Ready to discharge 30, 60, and 90 minutes post injection of the initial dose
- Drowsiness visual analogue scale to assess for signs of re-sedation
- Requirement for flumazenil during the procedure

- Patient's self-evaluation of "back-to-normal" after the procedure
- Pain on injection at application of study medication
- Population PK (pharmacokinetics) in patients below 65 years of age, and patients aged 65-74

Table 2: Description of Modified Observer's Alertness/Sedation (MOAA/S) Scale Scores

Score	**Description**
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Table 3: Study Inclusion and Exclusion Criteria

Inclusion Criteria

- Male and female patients, aged ≥18, scheduled to undergo a diagnostic or therapeutic colonoscopy (therapeutic procedures may include hemostasis, resection, ablation decompression, foreign body extraction, for example).
- American Society of Anesthesiologists Score 1 through 3.
- Body mass index ≤40 kg/m^2.
- For female patients with child-bearing potential, negative result of pregnancy test (serum or urine) as well as use of birth control during the study period (from the time of consent until all specified observations are completed).
- Patient voluntarily signs and dates an Informed Consent Form that is approved by an Institutional Review Board before the conduct of any study procedure.
- Patient is willing and able to comply with study requirements and return for a follow-up visit on day 4 (+3/-1 days) after the colonoscopy.

Exclusion Criteria

- Patients with a known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that these agents are contraindicated.
- Chronic use of benzodiazepines for any indication (eg, insomnia, anxiety, spasticity).
- Chronic use of opioids for any indication.

- Female patients with a positive serum human chorionic gonadotropin pregnancy test at screening or baseline.
- Lactating female patients.
- Patients with positive drugs of abuse screen or a positive serum ethanol at baseline.
- Patient with a history of drug or ethanol abuse within the past 2 years.
- Patients in receipt of any investigational drug within 30 days or less than 7 half-lives (whichever is longer) before screening, or scheduled to receive one during the study period.
- Participation in any previous clinical trial with remimazolam.
- Patients with an inability to communicate well in English with the investigator, or deemed unsuitable according to the investigator (in each case providing a reason).

Table 4: *Demographics of the 3 study arms*

		Remimazolam	**Placebo**	**Midazolam**	**TOTAL**
		N=296 n (%)	N=60 n (%)	N=102 n (%)	N=458 n (%)
Age [years]	N	296	60	102	458
	Mean	54.4	56.0	55.6	54.9
	SD	10.12	9.51	10.15	10.05
	Minimum	19	24	20	19
	Median	55.0	56.0	57.0	55.5
	Maximum	80	92	74	92
Age Group [years]	<65	254 (85.8%)	53 (88.3%)	88 (86.3%)	395 (86.2%)
	≥65	42 (14.2%)	7 (11.7%)	14 (13.7%)	63 (13.8%)
Gender	Male	147 (49.7%)	25 (41.7%)	46 (45.1%)	218 (47.6%)
	Female	149 (50.3%)	35 (58.3%)	56 (54.9%)	240 (52.4%)
Race	American Indian or Alaska Native	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Asian	18 (6.1%)	3 (5.0%)	10 (9.8%)	31 (6.8%)
	Black or African American	52 (17.6%)	14 (23.3%)	14 (13.7%)	80 (17.5%)
	Native Hawaiian or Other Pacific Islander	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	White	220 (74.3%)	43 (71.7%)	76 (74.5%)	339 (74.0%)
	Other	3 (1.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
	Multiple	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Ethnicity	Hispanic or Latino	46 (15.5%)	10 (16.7%)	17 (16.7%)	73 (15.9%)
	Not Hispanic or Latino	250 (84.5%)	50 (83.3%)	85 (83.3%)	385 (84.1%)

		Remimazolam	Placebo	Midazolam	TOTAL
		N=296 n (%)	N=60 n (%)	N=102 n (%)	N=458 n (%)
Height [cm]	N	296	60	102	458
	Mean	170.1	167.8	169.5	169.6
	SD	10.36	10.24	11.15	10.53
	Minimum	144	147	143	143
	Median	170.0	166.0	170.0	170.0
	Maximum	193	193	200	200
Weight [kg]	N	296	60	102	458
	Mean	83.2	84.6	81.9	83.1
	SD	17.39	19.90	16.24	17.47
	Minimum	40	49	52	40
	Median	83.7	80.8	81.8	82.1
	Maximum	128	144	126	144
BMI [kg/m^2]	N	296	60	102	458
	Mean	28.9	30.0	28.8	29.0
	SD	4.72	5.31	4.75	4.81
	Minimum	17	19	17	17
	Median	29.1	29.0	28.2	28.7
	Maximum	40	40	39	40
ASA-PS score	N	296	60	102	458
	I	95	11	37	143
	II	179	45	61	285
	III	22	4	4	30

Table 5: Primary Efficacy Variable: Overall Procedural Success (ITT set)

	Remimazolam	**Placebo**	**Midazolam**
Procedure Success	91.3%	1.70%	25.2%
Colonoscopy Completed	97.7%	98.3%	98.1%
-*/No need for rescue medication	96.6%	5.0%	35.9%
No more than 5 "top-ups" in any 15 minute interval (for midazolam, 3 "top-ups" in any 12 minute interval)	94.0%	26.7%	45.6%

Comparison	**Difference in Rates**	**95% Confidence Interval**		***P*-Value**
		Lower	**Upper**	
Remimazolam vs Placebo	0.8961	0.8505	0.9416	<0.0001
Remimazolam vs Midazolam	0.6603	0.5705	0.7501	

Table 6: Fentanyl Dosing in the Study Arms

	Remimazolam	Placebo	Midazolam	*P* value for Remimazolam Versus Placebo
Received the 75 μg initial dose	79.7%	80.0%	77.5%	0.88
Mean total fentanyl-μg	88.6	121.3	106.9	.0000
Mean number of fentanyl top ups	0.76	1.93	1.34	.0000

Table 7: Mean Times for Recovery (Minutes)

	Remimazolam	Placebo	Midazolam	*P* value (remimazolam vs placebo)
From end of procedure to fully alert	7.35 (5.78)	21.95 (17.74)	15.84 (11.57)	<0.0001
From procedure and until walking test passed	43.81 (13.26)	54.50 (20.26)	48.75 (14.44)	<0.0001
From last study medication until walking test passed	50.94 (13.84)	65.10 (18.77)	58.07 (14.4)	<0.0001
From start of medication to ready-for-discharge	60.34 (13.7	87.95 (21.07)	77.27 (15.85)	<0.0001
End of study medication to back to normal	330.71 (484.09)	572.67 (626.75)	553.11 (502.92)	0.001
Time to fully alert from last dose of IMP/rescue [min]	14.36 (5.39)	31.93 (16.81)	25.19 (11.26)	<0.0001
Time to ready for discharge from end of procedure [min]	42.65 (13.74)	53.18 (20.55)	47.92 (14.68)	<0.0001
Time to ready for discharge from last dose of IMP/rescue [min]	49.78 (14.33	63.78 (19.09)	57.44 (14.56)	<0.0001

Table 8: Hopkins Verbal Learning Test Scores 5 Minutes After Full Alertness

Parameter/ Timepoint	**Comparison**	**Mean Difference Between Treatments**	**95% Confidence Interval**		***P* value**
			Lower	**Upper**	
Total Recall 5 minutes after fully alert	Remimazolam vs Placebo	4.69	2.52	6.86	<0.0001
	Remimazolam vs Midazolam	3.94	2.22	5.66	
Delayed Recall 5 minutes after fully alert	Remimazolam vs Placebo	3.74	-0.47	7.96	0.0816
	Remimazolam vs Midazolam	2.97	-0.16	6.09	
Retention 5 minutes after fully alert	Remimazolam vs Placebo	4.48	-2.82	11.79	0.2273
	Remimazolam vs Midazolam	4.58	-1.04	10.19	
RDI 5 minutes after fully alert	Remimazolam vs Placebo	6.35	2.25	10.46	0.0025
	Remimazolam vs Midazolam	7.43	4.53	10.33	

RDI = Recognition Discrimination Index

Note: Statistics (mean difference and confidence intervals based on Least Square Means and P value) are from analysis of variance with treatment and age group as main effects.

Table9: *Incidence of treatment emergent adverse events*

System Organ Class Preferred Term	Remimazolam N=296 n (%)	Placebo N=60 n (%)	Midazolam N=102 n (%)	Total N=458
Any treatment-emergent adverse events	218 (73.6%)	47 (78.3%)	93 (91.2%)	358 (78.2%)
Vascular disorders	184 (62.2%)	41 (68.3%)	83 (81.4%)	308 (67.2%)
Hypotension	115 (38.9%)	25 (41.7%)	63 (61.8%)	203 (44.3%)
Hypertension	59 (19.9%)	17 (28.3%)	18 (17.6%)	94 (20.5%)
Diastolic hypertension	29 (9.8%)	6 (10.0%)	9 (8.8%)	44 (9.6%)
Diastolic hypotension	23 (7.8%)	4 (6.7%)	9 (8.8%)	36 (7.9%)
Systolic hypertension	16 (5.4%)	5 (8.3%)	6 (5.9%)	27 (5.9%)
Cardiac disorders	53 (17.9%)	14 (23.3%)	26 (25.5%)	93 (20.3%)
Bradycardia	33 (11.1%)	7 (11.7%)	16 (15.7%)	56 (12.2%)
Tachycardia	23 (7.8%)	7 (11.7%)	13 (12.7%)	43 (9.4%)
Respiratory, thoracic and mediastinal disorders	11 (3.7%)	4 (6.7%)	6 (5.9%)	21 (4.6%)
Bradypnoea	4 (1.4%)	2 (3.3%)	3 (2.9%)	9 (2.0%)
Hypoxia	3 (1.0%)	2 (3.3%)	1 (1.0%)	6 (1.3%)
Respiratory depression	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Gastrointestinal disorders	8 (2.7%)	5 (8.3%)	3 (2.9%)	16 (3.5%)
Nausea	5 (1.7%)	4 (6.7%)	2 (2.0%)	11 (2.4%)
Vomiting	3 (1.0%)	2 (3.3%)	0 (0.0%)	5 (1.1%)
Diarrhoea	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Nervous system disorders	11 (3.7%)	0 (0.0%)	3 (2.9%)	14 (3.1%)
Headache	5 (1.7%)	0 (0.0%)	3 (2.9%)	8 (1.7%)
Dizziness	3 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)
Presyncope	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Investigations	8 (2.7%)	1 (1.7%)	4 (3.9%)	13 (2.8%)
Respiratory rate decreased	3 (1.0%)	0 (0.0%)	2 (2.0%)	5 (1.1%)

System Organ Class	Remimazolam	Placebo	Midazolam	Total
Preferred Term	N=296	N=60	N=102	N=458
	n (%)	n (%)	n (%)	
Blood pressure diastolic increased	3 (1.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
Blood pressure diastolic decreased	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Blood pressure systolic decreased	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Blood pressure systolic increased	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Haematocrit decreased	1 (0.3%)	1 (1.7%)	0 (0.0%)	2 (0.4%)
Haemoglobin decreased	1 (0.3%)	1 (1.7%)	0 (0.0%)	2 (0.4%)
Infections and infestations	2 (0.7%)	1 (1.7%)	1 (1.0%)	4 (0.9%)
General disorders and administration site conditions	2 (0.7%)	0 (0.0%)	1 (1.0%)	3 (0.7%)
Metabolism and nutrition disorders	2 (0.7%)	0 (0.0%)	1 (1.0%)	3 (0.7%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Contusion	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Back pain	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Eye disorders	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.2%)
Psychiatric disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Skin and subcutaneous tissue disorders	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.2%)

Table 10: *Continuous Monitoring of Vital Signs - Nadirs (Applicable Safety [Nellcor] Populations)*

Parameter	Sample	Remimazolam	Placebo	Midazolam	Total
	Characteristics				
Heart Rate (beats/minute)	N	214	40	71	325
	Mean	61.5	59.3	57.5	60.4
	Std. Deviation	10.90	10.58	7.99	10.40
	Minimum	34	38	40	34
	Lower Quartile	55.0	52.0	53.0	54.0
	Median	61.0	59.0	57.0	59.0
	Upper Quartile	68.0	65.5	64.0	66.0
	Maximum	100	86	81	100
Respiratory Rate (breaths/minute) - Lowest Nellcor Value (calculated)	N	116	19	37	172
	Mean	10.3	8.9	9.2	9.9
	Std. Deviation	2.43	2.61	1.99	2.42
	Minimum	5	6	5	5
	Lower Quartile	9.0	7.0	8.0	8.0
	Median	11.0	8.0	9.0	10.0
	Upper Quartile	12.0	11.0	10.0	12.0
	Maximum	19	15	14	19
Oxygen Saturation (%) – Lowest Nellcor Value (calculated)	N	216	42	71	329
	Mean	93.5	88.5	93.1	92.7
	Std. Deviation	5.71	9.07	6.53	6.59
	Minimum	63	56	65	56
	Lower Quartile	91.0	87.0	91.0	90.0
	Median	95.0	91.0	95.0	95.0
	Upper Quartile	97.0	94.0	97.0	97.0
	Maximum	100	98	100	100

Figures

Figure 1: Study Diagram

Supplementary Material

Supplementary Table 1: Day 1 – Assessments based on dosing time

Dosing Day (Day 1)																			
Procedures	**Pre-dose**				**Dosing of trial medication[1]**	**Post-dose**													
	within 3 hr	**within 30 min.**	**within 15 min.**	**1min. pre-dose**		**1 min.**	**1.5 min.**	**2 min.**	**2.5 min.**	**3 min.**	**5 min.**	**10 min.**	**Every 5 minutes until fully alert**						
Review inclusion & exclusion criteria	X																		
Medical & medication histories	X																		
Adverse Events	X																		
Concomitant medication	X																		
Physical examination	x (B)																		
Weight	x (B)																		
Body temperature	x (B)	x									x (post pro-cedure)			x (at fully alert)				x (at discharge)	
Clinical laboratory tests	x (B)																	x (at discharge)	
3 lead ECG			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
3 lead ECG documentation in CRF [5]			x	x				x			x	x	x	x	x	x	x	x	
12-lead ECG	x (B)					x					x		x[6]		x[6]		x[6]		
Urine pregnancy test	X																		
Urine drug-of abuse test	X																		
Ethanol saliva test	X																		
Randomization	X																		
HVLT-R	Learning	(within 45 min)									x								

Dosing Day (Day 1)																		
Procedures	**Pre-dose**				**Dosing of trial medication[1]**	**Post-dose**												
	within 3 hr	**within 30 min.**	**within 15 min.**	**1min. pre-dose**		**1 min.**	**1.5 min.**	**2 min.**	**2.5 min.**	**3 min.**	**5 min.**	**10 min.**	**Every 5 minutes until fully alert**					
Hemodynamic parameters (HR, BP)[7,8]	X	x	x (B)	x				x			x	x	x	x	x	x	x	x
Normal saline		xx	xx	xx	XX up to 1000 mL administered, if fluid status allows	xx	xx	xx	xx	xx	xx	xx	xx	until end of colonoscopy procedure				
MOAA/S[2]			x (B)			x	x	x	x	every minute until fully alert, then every 5 min until ready for discharge, then every 10 min until actual discharge								
Respiratory rate[8]			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
RR (document in CRF)			x (B)	x				x			x	x	x	x	x	x	x	x	x
SpO_2[3] (pulse oximetry)			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
SpO_2[7,8] (documentation in CRF)			x (B)	x				x			x	x	x	x	x	x	x	x	x
Airway management assessment			x																
Supplemental O_2 (nasal prongs)			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Fentanyl					x	Supplemental doses q 5-10 min until adequate analgesia or 200 µg maximum dose													
Pain on injection	Learning				x or as soon as poss..														
Drowsiness VAS[4]				x				x			x	x	15		25	35	45	60	
Brice												x (within 10 mins)							

(B) = Baseline values, x = Single action, xx = Continuous action, mins = minutes CRF case report form, HR heart rate, BP blood pressure, RR respiratory rate, VAS visual analogue scale

NOTE: [1] Trial medication: Loading dose of randomized study drug start defines t=0, supplemental doses as per protocol.
[2] Colonoscopy starts at sufficient sedation (MOAA/S ≤3), duration as necessary (MOAA/S ≤4), at the discretion of the investigator.
[3] 90 minute value only if patient is still sedated.

[4] If possible by patient.
[5] Documented by running a strip.
[6] after first dose, 5 minutes after dosing and every 10 minutes until the end of the procedure if possible, and also 5 minutes after the end of the procedure.
[7] In addition to the times specified above, blood pressure, heart rate, and SpO_2 will be recorded immediately before, and 2 minutes after each additional dose of fentanyl
[8] Vital signs (heart rate, systolic and diastolic BP, respiratory rate, and SpO_2) will be recorded when an AE with a respiratory or cardiovascular focus has been observed.

Supplementary Table 2: Analysis Sets and Populations Across Groups

Analysis Sets	**Remimazolam** N=298 n (%)	**Placebo** N=60 n (%)	**Midazolam** N=103 n (%)	**TOTAL** N=461 n (%)
Randomized	298 (100.0%)	60 (100.0%)	103 (100.0%)	461 (100.0%)
Safety Population[a]	296 (99.3%)	60 (100.0%)	102 (99.0%)	458 (99.3%)
Safety Population (Nellcor) - At least one Parameter usable[b]	216 (72.5%)	42 (70.0%)	71 (68.9%)	329 (71.4%)
Safety Population (Nellcor) - Usable Heart Rate[b1]	214 (71.8%)	40 (66.7%)	71 (68.9%)	325 (70.5%)
Safety Population (Nellcor) - Usable Respiratory Rate[b2]	116 (38.9%)	19 (31.7%)	37 (35.9%)	172 (37.3%)
Safety Population (Nellcor) - Usable Oxygen Saturation[b3]	216 (72.5%)	42 (70.0%)	71 (68.9%)	329 (71.4%)
Intention-to-treat Analysis Set[c]	298 (100.0%)	60 (100.0%)	103 (100.0%)	461 (100.0%)
Modified Intention-to-treat Analysis Set[d]	296 (99.3%)	60 (100.0%)	102 (99.0%)	458 (99.3%)
Per-Protocol Analysis Set[e]	228 (76.5%)	44 (73.3%)	77 (74.8%)	349 (75.7%)

N = number of patients; n = number of observations
a The Safety Population consists of all randomized patients who received any amount of study drug and were analyzed as treated.
b Safety Population (Nellcor) consists of all patients in the Safety Population who had usable Nellcor data in at least one parameter
b1 Consists of all patients in the Safety Population who had usable Heart Rate data (Nellcor)
b2 Consists of all patients in the Safety Population who had usable Respiratory Rate data (Nellcor)
b3 Consists of all patients in the Safety Population who had usable Oxygen Saturation data (Nellcor)
c The Intent-to-treat analysis set (ITT) includes all patients who were randomized and were analyzed as randomized.
d The Modified Intent-to-treat analysis set (mITT) includes all patients in the ITT population who received at least one complete dose of study medication.

Supplementary Table 3: Power Attained at Different Success Rates for the Placebo and Remimazolam Groups*

Placebo \ **Remimazolam**	**20%**	**25%**	**30%**
60%	100%	99.96%	99.33%
70%	100%	100%	100%
80%	100%	100%	100%
90%	100%	100%	100%

*type I error rate fixed as 0.025):

Supplementary Table 4: *Mean and SD of Vital Signs Reported by the Nellcor by Treatment arm at Different Sedation Levels*

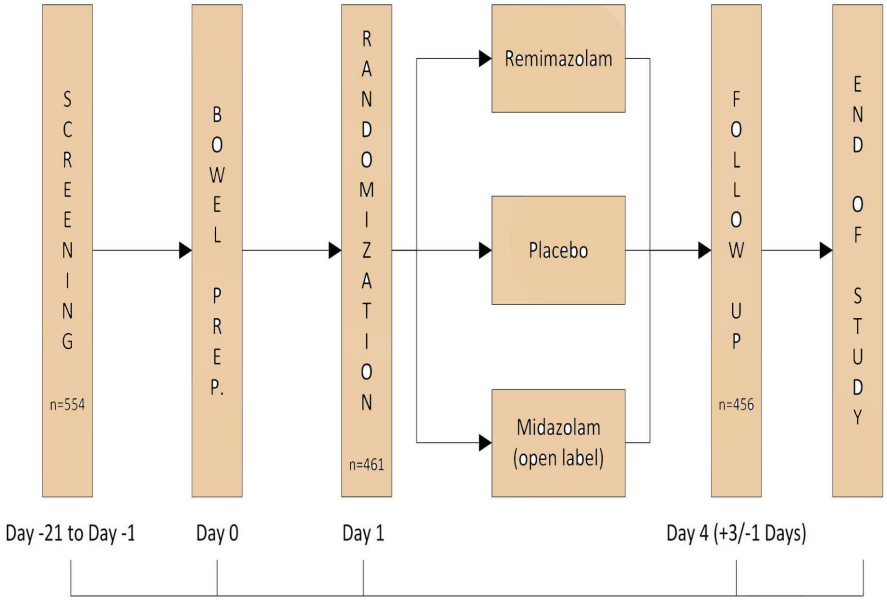
Heart Rate (beats/minute)					
Sedation Level	Treatment arm	Count	Mean	Median	SD
MOAA/S 0-1	MIDAZOLAM	27	58.52	61	7.97
	PLACEBO	26	64.15	64	4.62
	REMIMAZOLAM	328	67	66	10.66
MOAA/S 2-4	MIDAZOLAM	2590	63.51	63	9.12
	PLACEBO	1676	66.58	67	11.16
	REMIMAZOLAM	4708	68.74	68	11.6
MOAA/S 5	MIDAZOLAM	1258	66.07	65	10.6
	PLACEBO	1013	67.96	68	11.57
	REMIMAZOLAM	2143	65.75	64	11.94
Respiratory Rate (breath/minute)					
Sedation Level		Count	Mean	Median	SD
MOAA/S 0-1	MIDAZOLAM	25	11.36	11	2.14
	PLACEBO	23	13.43	14	4.52
	REMIMAZOLAM	309	12.57	12	2.41
MOAA/S 2-4	MIDAZOLAM	2260	13.12	13	3.58
	PLACEBO	1347	13.98	14	3.57
	REMIMAZOLAM	4246	13.63	13	3.4
MOAA/S 5	MIDAZOLAM	1043	12.56	12	3.33
	PLACEBO	847	12.91	13	3.51
	REMIMAZOLAM	1922	13.03	13	3.64
SpO2 (%)					
Sedation Level		Count	Mean	Median	SD
MOAA/S 0-1	MIDAZOLAM	27	99.11	99	0.89
	PLACEBO	26	95.96	97	2.14
	REMIMAZOLAM	328	97.99	99	3.09
MOAA/S 2-4	MIDAZOLAM	2590	97.55	98	2.92

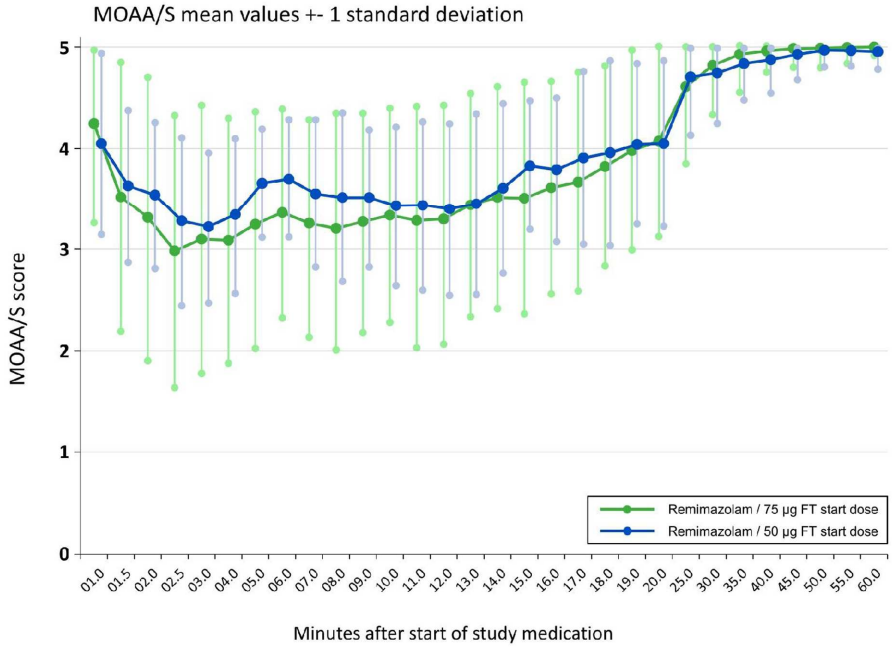
	PLACEBO	1679	97.11	98	3.86
	REMIMAZOLAM	4713	97.73	99	2.99
MOAA/S 5	MIDAZOLAM	1259	97.14	98	4.03
	PLACEBO	1015	97.63	99	3.74
	REMIMAZOLAM	2146	96.27	97	4.23

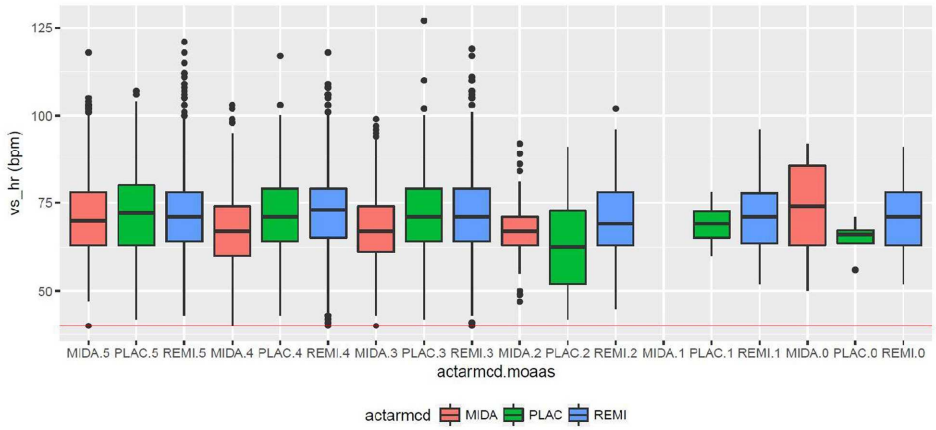
Supplementary Figure 1: Comparison of MOAA/S - Remimazolam plus fentanyl 75 vs 50 µg

Supplementary Figure 2: Analysis of Variance of Vital Signs by MOAA/S and by Treatment Arm

Red lines are marking the defined the thresholds defined for reporting AEs. Figure A, Heart Rate. B, Respiratory Rate. C, SpO_2.







Threshold red line at ≤ 40bpm